ClinicalEvidence

Herpes labialis

Search date February 2009

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ABSTRACT

INTRODUCTION: Herpes simplex virus type 1 infection usually causes a mild, self-limiting painful blistering around the mouth, with 20% to 40% of adults affected at some time. Primary infection usually occurs in childhood, after which the virus is thought to remain latent in the trigeminal ganglion. Recurrence may be triggered by factors such as exposure to bright light, stress, and fatigue. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of antiviral treatments for the first attack of herpes labialis? What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis? What are the effects of treatments for recurrent attacks of herpes labialis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 27 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: oral antiviral agents, sunscreen, topical anaesthetic agents, topical antiviral agents, and zinc oxide cream.

QUESTIONS

What are the effects of antiviral treatments for the first attack of herpes labialis? . . . 3

What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis? . . . 5

What are the effects of treatments for recurrent attacks of herpes labialis? . . . 13

INTERVENTIONS

TREATING THE FIRST ATTACK

Likely to be beneficial

Oral antiviral agents (aciclovir) . . . 3

Unknown effectiveness

Topical antiviral agents . . . 4

PREVENTING RECURRENT ATTACKS

Likely to be beneficial

Oral antiviral agents (aciclovir) . . . 5

Sunscreen . . . 12

Unknown effectiveness

Topical antiviral agents . . . 9

TREATING RECURRENT ATTACKS

Likely to be beneficial

Oral antiviral agents (aciclovir, famciclovir, and valaciclovir) . . . 13

Unknown effectiveness

Topical anaesthetic agents . . . 21

Topical antiviral agents (some evidence of statistical benefit, but benefit is of marginal clinical importance) . . . 18

Zinc oxide cream . . . 22

Key points

- Herpes simplex virus type 1 infection usually causes a mild, self-limiting painful blistering around the mouth, with 20% to 40% of adults affected at some time.

  Primary infection usually occurs in childhood, after which the virus is thought to remain latent in the trigeminal ganglion.

  Recurrence may be triggered by factors such as exposure to bright light, stress, and fatigue.

- Oral antiviral agents such as aciclovir may reduce the duration of pain and time to healing for a first attack of herpes labialis compared with placebo; however, evidence is limited.

  We don't know whether topical antiviral agents can reduce pain or time to healing in a first attack.

- Prophylactic oral antiviral agents may reduce the frequency and severity of attacks compared with placebo, but we don't know the best timing and duration of treatment.

  We don't know whether topical antiviral treatments are beneficial as prophylaxis against recurrent attacks.

  Ultraviolet sunscreen may reduce recurrent attacks; however, evidence is limited.

- Oral antiviral agents may reduce the duration of symptoms and the time to heal in recurrent attacks of herpes labialis.

  Oral aciclovir, famciclovir, and valaciclovir may marginally reduce healing time if taken early in a recurrent attack, but valaciclovir may cause headache.

- We found limited evidence that topical antiviral agents may reduce pain and healing time in recurrent attacks. However, results are inconsistent and of marginal clinical importance.
- We don't know whether topical anaesthetic agents or zinc oxide cream reduce healing time. Zinc oxide cream may increase skin irritation.

DEFINITION

Herpes labialis is a mild, self-limiting infection with herpes simplex virus type 1 (HSV-1). It causes pain and blistering on the lips and perioral area (cold sores); fever and constitutional symptoms are rare. Most people have no warning of an attack, but some experience a recognisable prodrome. In this review, we have included studies in people with normal immunity and excluded studies in people who are immunocompromised (e.g., studies in people with HIV or with cancer undergoing chemotherapy).

INCIDENCE/ PREVALENCE

Herpes labialis accounts for about 1% of primary care consultations in the UK each year; 20% to 40% of people have experienced cold sores at some time. [1]

AETIOLOGY/ RISK FACTORS

Herpes labialis is caused by HSV-1. After the primary infection, which usually occurs in childhood, the virus is thought to remain latent in the trigeminal ganglion. [2] A variety of factors, including exposure to bright sunlight, fatigue, or psychological stress, can precipitate a recurrence.

PROGNOSIS

In most people, herpes labialis is a mild, self-limiting illness. Recurrences are usually shorter and less severe than the initial attack. Healing is usually complete in 7 to 10 days without scarring. [3] Rates of reactivation are unknown. Herpes labialis can cause serious illness in immunocompromised people.

AIMS OF INTERVENTION

To reduce the frequency and severity of recurrent attacks; to speed healing of lesions; to reduce pain, with minimal adverse effects.

OUTCOMES

Symptom improvement (severity of symptoms and duration of symptoms; does not include time to healing or crusting of lesions); **time to healing** (time to healing/time to crusting of lesions); **rate of recurrence**; **quality of life**; **adverse effects of treatment**.

METHODS

Clinical Evidence search and appraisal February 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2009, Embase 1980 to February 2009, and The Cochrane Database of Systematic Reviews, 2009, Issue 1 (1966 to date of issue). An additional search within the Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 26). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of antiviral treatments for the first attack of herpes labialis?

OPTION ORAL ANTIVIRAL AGENTS FOR FIRST ATTACK

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- Oral antiviral agents such as aciclovir may reduce the duration of pain and time to healing for a first attack of herpes labialis compared with placebo; however, evidence is limited.

Benefits and harms

Oral antiviral agents versus placebo:

We found two small RCTs in children. [4] [5] We found no RCTs in adults.

Symptom improvement

Oral antiviral agents compared with placebo Oral aciclovir may be more effective at marginally reducing the mean duration of pain in children of mean age 2 years with herpetic gingivitis–stomatitis of <4 days' duration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[4] RCT	20 children, mean age 2 years, with herpetic gingivi-tis–stomatitis of less than 4 days' duration	**Mean duration of pain** 4.3 days with oral aciclovir (200 mg 5 times daily) 5.0 days with placebo	P = 0.05	○○○	oral aciclovir

No data from the following reference on this outcome. [5]

Time to healing

Oral antiviral agents compared with placebo Oral aciclovir may be more effective at reducing the median time to healing in children aged 1 to 6 years with herpes simplex gingivitis–stomatitis of <3 days' duration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[5] RCT	72 children, aged 1 to 6 years, with herpes simplex gingivitis–stomatitis of <3 days' dura-tion	**Median time to healing** 4 days with oral aciclovir (15 mg/kg 5 times daily for 7 days) 10 days with placebo	Median difference 6 days 95% CI 4 days to 8 days	○○○	oral aciclovir

No data from the following reference on this outcome. [4]

Recurrence

No data from the following reference on this outcome. [4] [5]

Quality of life

No data from the following reference on this outcome. [4] [5]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[4] RCT	20 children of mean age 2 years with herpetic gingivitis–stomatitis of <4 days' duration	**Adverse effects** with oral aciclovir (200 mg 5 times daily) with placebo Reported that there were no significant adverse effects in either group			
[5] RCT	72 children aged 1 to 6 years with herpes simplex gingivitis–stomatitis of <3 days' duration	**Adverse effects** with oral aciclovir (15 mg/kg 5 times daily for 7 days) with placebo Reported that there were no significant adverse effects in either group			

Further information on studies

Comment: Oral aciclovir is excreted in breast milk. Aciclovir has been used to treat pregnant women with genital herpes, and one systematic review (search date 1996, 3 RCTs) found no evidence of adverse effects in women or newborn children (see antiviral treatment during pregnancy in the genital herpes review). [6] However, evidence is limited and clinically important adverse effects cannot be ruled out.

Research in this area is difficult because people may not consult clinicians until they have experienced several attacks of herpes labialis.

OPTION TOPICAL ANTIVIRAL AGENTS FOR FIRST ATTACK

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- We don't know whether topical antiviral agents can reduce pain or time to healing in a first attack.

Benefits and harms

Topical antiviral agents versus placebo:

We found no RCTs comparing topical antiviral agents versus placebo or no treatment.

Further information on studies

Comment: Trials have found that topical aciclovir is associated with rash, pruritus, and irritation in some people, but no more frequently than placebo. [6] [7] [8]

Research in this area is difficult because people may not consult clinicians until they have experienced several attacks of herpes labialis.

QUESTION What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis?

OPTION ORAL ANTIVIRAL AGENTS TO PREVENT RECURRENCE

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- Prophylactic oral antiviral agents may reduce the frequency and severity of attacks compared with placebo, but we don't know the best timing and duration of treatment.

Benefits and harms

Oral antiviral agents versus placebo:

We found one systematic review (search date 2008), [9] which included three RCTs [10] [11] [12] and one pooled analysis of two further RCTs. [13] We found one additional RCT. [14] The review did not pool data and did not report a methodological appraisal or a statistical analysis of individual RCTs. Therefore, we have reported the RCTs from their original reports.

Symptom improvement

Oral antiviral agents compared with placebo Prophylactic oral aciclovir may be more effective at reducing the duration of symptoms in US skiers with a history of herpes labialis precipitated by ultraviolet light (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[10] RCT	147 US skiers with a history of herpes labialis precipitated by ultraviolet light In review [9]	**Duration of symptoms** with aciclovir (400 mg twice daily, starting 12 hours before ultraviolet exposure) with placebo	P <0.05	○○○	aciclovir

No data from the following reference on this outcome. [11] [12] [13] [14]

Time to healing

Oral antiviral agents versus placebo Oral famciclovir may be more effective at reducing the mean time to healing in adults with a history of sun-induced recurrent herpes labialis (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis The remaining arms evaluated famciclovir (125 mg) and famciclovir (250 mg)	**Duration of lesions** with famciclovir (500 mg) with placebo Absolute results not reported Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reduction in healing time 2 days with famciclovir P = 0.01 for famciclovir 500 mg *v* placebo	○○○	famciclovir (500 mg)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis The remaining arms evaluated famciclovir (250 mg) and famciclovir (500 mg)	**Duration of lesions** with famciclovir (125 mg) with placebo Absolute results not reported Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reported as not significant P value not reported for famciclovir 125 mg *v* placebo	⟷	Not significant
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis The remaining arms evaluated famciclovir (125 mg) and famciclovir (500 mg)	**Duration of lesions** with famciclovir (250 mg) with placebo Absolute results not reported Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reported as not significant P value not reported for famciclovir 250 mg *v* placebo	⟷	Not significant
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis The remaining arms evaluated famciclovir (125 mg) and famciclovir (250 mg)	**Size of lesions** with famciclovir (500 mg) with placebo Absolute results not reported Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	P = 0.04 for famciclovir 500 mg *v* placebo	○○○	famciclovir (500 mg)
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis The remaining arms evaluated evaluated famciclovir (250 mg) and famciclovir (500 mg)	**Size of lesions** with famciclovir (125 mg) with placebo Absolute results not reported Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reported as not significant P value not reported for famciclovir 125 mg *v* placebo	⟷	Not significant
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis The remaining arms evaluated evaluated famciclovir (125 mg) and famciclovir (500 mg)	**Size of lesions** with famciclovir (250 mg) with placebo Absolute results not reported Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Reported as not significant P value not reported for famciclovir 250 mg *v* placebo	⟷	Not significant

No data from the following reference on this outcome. [10] [11] [12] [13]

Recurrence

Oral antiviral agents compared with placebo Prophylactic oral aciclovir may be more effective at reducing the frequency of attacks, but not at reducing lesion occurrence (not further defined). Oral famciclovir may be no more effective at reducing the number of lesions in adults with a history of sun-induced recurrent herpes labialis. Oral valaciclovir may be more effective at reducing the proportion of people with recurrence within 4 months and at increasing the time to recurrence in adults with a history of four or more attacks in the previous year (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[10] RCT	147 US skiers with a history of herpes labialis precipitated by ultraviolet light In review [9]	**Frequency of attacks** with aciclovir (400 mg twice daily, starting 12 hours before ultraviolet exposure) with placebo	P <0.05	○○○	aciclovir
[11] RCT	239 Canadian skiers with a history of recurrent herpes labialis In review [9]	**Lesion occurrence** 21/93 (23%) with aciclovir (800 mg twice daily) 21/102 (21%) with placebo Aciclovir was started on the day before exposure to ultraviolet light for a minimum of 3 days to a maximum of 7 days All participants were allowed to use paracetamol (acetaminophen) and encouraged to use sunscreen	P = 0.92	⟷	Not significant
[12] RCT	20 people with recurrent herpes labialis In review [9]	**Clinical recurrences** with aciclovir (400 mg twice daily for 4 months) with placebo	53% fewer attacks with aciclovir P = 0.05	○○○	aciclovir
[13] pooled analysis of two RCTs	98 adults with a history of 4 or more attacks in the previous year	**No recurrence , 4 months** 62% with oral valaciclovir 500 mg daily 40% with placebo	P = 0.041	○○○	valaciclovir
[13] pooled analysis of two RCTs	98 adults with a history of 4 or more attacks in the previous year	**Mean time to recurrence** 13.1 weeks with oral valaciclovir 500 mg daily 9.6 weeks with placebo	P = 0.016	○○○	valaciclovir
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis	**Number of lesions** with famciclovir (125 mg) with famciclovir (250 mg) with famciclovir (500 mg) with placebo Treatment was given three times daily for 5 days, beginning 48 hours after exposure to artificial ultraviolet light	Difference among groups reported as not significant (between group differences not assessed) P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [10] [11] [12] [13] [14]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] RCT	147 US skiers with a history of herpes labialis precipitated by ultraviolet light In review [9]	**Mild to moderate central nervous system or gastrointestinal tract adverse events** 7/77 (9%) with aciclovir (400 mg twice daily, starting 12 hours before ultraviolet exposure) 3/76 (4%) with placebo	P = 0.34	⟷	Not significant
[11] RCT	239 Canadian skiers with a history of recurrent herpes labialis In review [9]	**Rates of adverse events** 58/115 (50%) with aciclovir (800 mg twice daily) 59/124 (48%) with placebo Headache and nausea were the most common adverse effects reported Aciclovir was started on the day before exposure to ultraviolet light for a minimum of 3 days to a maximum of 7 days All participants were allowed to use paracetamol (acetaminophen) and encouraged to use sunscreen	P = 0.68	⟷	Not significant
[11] RCT	239 Canadian skiers with a history of recurrent herpes labialis In review [9]	**Number of severe adverse events** 5 with aciclovir (800 mg twice daily) 6 with placebo Severe adverse effects associated with aciclovir were knee throbbing, constipation, cold sore discomfort, stomach ache, and depression Severe adverse effects associated with placebo were insomnia, diarrhoea, and headache (4 people) Aciclovir was started on the day before exposure to ultraviolet light for a minimum of 3 days to a maximum of 7 days All participants were allowed to use paracetamol (acetaminophen) and encouraged to use sunscreen			
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis	**Headache or nausea (most common adverse events)** with famciclovir (125 mg) with famciclovir (250 mg) with famciclovir (500 mg) with placebo Absolute results not reported	Difference among groups reported as not significant (between group differences not assessed) P value not reported	⟷	Not significant
[14] RCT **4-armed trial**	248 adults with a history of sun-induced recurrent herpes labialis	**Severe adverse events, within 30 days of the last dose of famciclovir** with famciclovir (125 mg) with famciclovir (250 mg)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with famciclovir (500 mg) with placebo Absolute results not reported The analysis reported that no severe adverse events occurred in any group			
[13] pooled analysis of two RCTs	98 adults with a history of 4 or more attacks in the previous year	**Adverse events** 22 events in 33% of people with valaciclovir 29 events in 39% of people with placebo Most common adverse effect reported was mild headache None of the adverse events in the valaciclovir group and only three in the placebo group were reported to be treatment related			

No data from the following reference on this outcome. [12]

Further information on studies

Comment: None.

OPTION TOPICAL ANTIVIRAL AGENTS TO PREVENT RECURRENCE

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- We don't know whether topical antiviral treatments are beneficial as prophylaxis against recurrent attacks.

Benefits and harms

Topical antiviral agents versus placebo:

We found one systematic review (search date 2008) [9] identifying two RCTs. [15] [16] The review did not pool data, and did not report a methodological appraisal or a statistical analysis of individual RCTs. Therefore, we have reported the RCTs from their original reports. See harms under the effects of antiviral treatments for the first attack, p 4 .

Symptom improvement

Topical antivirals compared with placebo We don't know whether prophylactic aciclovir cream is more effective than placebo cream at reducing the duration of pain in people with herpes labialis precipitated by exposure to sunlight (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[15] RCT	90 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [9]	**Mean duration of pain** 3.7 days with aciclovir cream 3.6 days with placebo cream Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure	P >0.10 Results should be interpreted with care, as the RCT was conducted under artificial conditions	⟷	Not significant

No data from the following reference on this outcome. [16]

Time to healing

Topical antivirals compared with placebo We don't know whether prophylactic aciclovir cream is more effective than placebo cream at reducing mean healing time in people with herpes labialis precipitated by exposure to sunlight (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[15] RCT	90 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [9]	**Mean healing time to loss of crust** 6.7 days with aciclovir cream 6.5 days with placebo cream Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure	P = 0.79 Results should be interpreted with care as the RCT was conducted under artificial conditions	⟷	Not significant
[15] RCT	90 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [9]	**Mean healing time to normal skin** 6.8 days with aciclovir cream 7.4 days with placebo cream Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure	P = 0.70 Results should be interpreted with care, as the RCT was conducted under artificial conditions	⟷	Not significant

No data from the following reference on this outcome. [16]

Recurrence

Topical antivirals compared with placebo We don't know whether prophylactic aciclovir cream is more effective than placebo cream at reducing recurrence in people with herpes labialis precipitated by exposure to sunlight (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[15] RCT	90 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [9]	**People developing lesions** 22/45 (49%) with aciclovir cream 18/45 (40%) with placebo cream Lips were exposed to ultraviolet light to induce a recurrence of herpes labialis Cream applied for 7 days immediately after ultraviolet light exposure	Significance not assessed Results should be interpreted with care, as the RCT was conducted under artificial conditions		
[16] RCT	196 skiers aged 18 years or over, with 3 episodes of sun-induced herpes labialis during the previous year In review [9]	**Proportion of people with lesions during the treatment period** 15/91 (16%) with aciclovir cream 23/90 (26%) with placebo cream Cream was applied 12 hours before intensive sun exposure and continued for between 72 to 168 hours	P = 0.2	⟷	Not significant
[16] RCT	196 skiers aged 18 years or over, with 3 episodes of sun-induced herpes labialis during the previous year In review [9]	**Proportion of people with lesions during the 4-day follow-up period after treatment** 18/91 (20%) with aciclovir cream 35/90 (39%) with placebo cream Cream was applied 12 hours before intensive sun exposure and continued for between 72 to 168 hours	P <0.01	○○○	aciclovir cream

Quality of life

No data from the following reference on this outcome. [15] [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	90 people, aged 18 years or older, with a history of herpes labialis precipitated by exposure to sunlight In review [9]	**Adverse effects** with aciclovir cream with placebo cream Absolute results not reported No local or systemic adverse reactions to treatment reported			
[16] RCT	196 skiers aged 18 years or over, with 3 episodes of sun-induced herpes labialis during the previous year In review [9]	**People reporting at least one adverse effect (not further defined)** 15/95 (16%) with aciclovir cream 13/96 (14%) with placebo cream	Reported as not significant P value not reported	⟷	Not significant

Further information on studies

Comment: None.

OPTION SUNSCREEN

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- Ultraviolet sunscreen may reduce recurrent attacks; however, evidence is limited.

Benefits and harms

Sunscreen versus placebo:

We found one systematic review (search date 2008) [9] including one RCT of sufficient quality. [17] We found one additional RCT. [18]

Symptom improvement

No data from the following reference on this outcome. [17] [18]

Time to healing

No data from the following reference on this outcome. [17] [18]

Recurrence

Sunscreen compared with placebo Sunscreen may be more effective at decreasing the proportion of people with recurrence at 6 days (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[17] RCT **Crossover design**	38 people with a history of recurrent herpes In review [9]	**Recurrence , 6 days** 0/35 (0%) with sunscreen 27/38 (71%) with placebo	P <0.001 Results should be interpreted with caution as crossover designs have important limitations	○○○	sunscreen
[18] RCT **Crossover design**	19 people exposed to a pre-established dose of ultraviolet light in a laboratory	**Recurrence , at 6 days** 1/19 (5%) with sunscreen 11/19 (58%) with placebo	P <0.01 Results should be interpreted with caution as crossover designs have important limitations and the RCT was conducted under artificial conditions	○○○	sunscreen

Quality of life

No data from the following reference on this outcome. [17] [18]

Adverse effects

No data from the following reference on this outcome. [17] [18]

Further information on studies

Comment: None.

QUESTION What are the effects of treatments for recurrent attacks of herpes labialis?

OPTION ORAL ANTIVIRAL AGENTS FOR TREATING RECURRENT ATTACKS

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- Oral antiviral agents may reduce the duration of symptoms and the time to heal in recurrent attacks of herpes labialis.
- Oral aciclovir, famciclovir, and valaciclovir may marginally reduce healing time if taken early in a recurrent attack, but valaciclovir may cause headache.

Benefits and harms

Oral antiviral agents versus placebo:

We found one systematic review (search date 2008), [9] which found five RCTs (published in 4 papers). [19] [20] [21] [22] The review did not pool data and did not report a methodological appraisal or a statistical analysis of individual RCTs. Therefore, we have reported the RCTs from their original reports.

Symptom improvement

Oral antiviral agents compared with placebo Oral aciclovir taken early in the attack (when the person first experiences tingling) may be more effective at reducing the duration of symptoms (not further defined) in adults with recurrent herpes labialis. Oral aciclovir taken within 12 hours of the onset of the first episode may be no more effective at reducing the duration of pain. We don't know whether oral famciclovir is more effective at reducing the median time to resolution of pain or tenderness in people aged 18 years or older with recurrent herpes labialis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[19] RCT	174 adults with recurrent herpes labialis In review [9]	**Duration of symptoms** 8.1 days with oral aciclovir (400 mg 5 times daily for 5 days) 12.5 days with placebo Aciclovir was taken early in the attack (when the person first experienced tingling)	P = 0.02	○○○	oral aciclovir
[20] RCT	149 people In review [9]	**Mean duration of pain** 1.31 days with aciclovir 1.35 days with placebo Aciclovir was taken within 12 hours of the onset of the first episode	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **3-armed trial**	701 people aged 18 years or older with recurrent herpes labialis In review [9] The remaining arm evaluated famciclovir as two doses on 1 day	**Median time to resolution of pain and tenderness** with famciclovir (as single dose on 1 day) with placebo Absolute results not reported Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions	P <0.01 for famciclovir as single dose on 1 day *v* placebo Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)	○○○	famciclovir (as single dose on 1 day)
[22] RCT	701 people aged 18 years or older with recurrent herpes labialis In review [9] The remaining arm evaluated famciclovir (as single dose on 1 day)	**Median time to resolution of pain and tenderness** with famciclovir as two doses on 1 day with placebo Absolute results not reported Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions.	P = 0.54 for famciclovir as two doses on 1 day *v* placebo Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)	⟷	Not significant

Time to healing

Oral antiviral agents compared with placebo Oral valaciclovir may be more effective at marginally reducing the median duration of the episode in people aged at least 12 years old with recurrent herpes labialis. Oral famciclovir may be more effective than placebo at reducing the median time to healing in people aged 18 years or older with recurrent herpes labialis, but not at increasing the proportion of people with aborted (not progressing beyond papule stage) lesions. Oral aciclovir taken within 12 hours of the onset of the first episode may be no more effective at reducing healing time (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[20] RCT	149 people In review [9]	**Mean healing time** 7.78 days with aciclovir 8.64 days with placebo Aciclovir was taken within 12 hours of the onset of the first episode	Reported as not significant P value not reported	⟷	Not significant
[21] RCT **3-armed trial**	902 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication The third arm evaluated 2-day course of valaciclovir (2 g twice daily for the first day followed by 1 g twice daily for the second day)	**Median duration of episode** 4.0 days with 1-day course of valaciclovir (2 g twice daily) 5.0 days with placebo	P <0.001 for 1-day course of valaciclovir *v* placebo	○○○	oral valaciclovir

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] RCT **3-armed trial**	902 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication The third arm evaluated 1-day course of valaciclovir (2 g twice daily)	**Median duration of episode** 4.5 days with 2-day course of valaciclovir (2 g twice daily for the first day followed by 1 g twice daily for the second day) 5.0 days with placebo	P = 0.009 for 2-day course of valaciclovir *v* placebo	○○○	oral valaciclovir
[21] RCT	954 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication The third arm evaluated 2-day course of valaciclovir (2 g twice daily for the first day followed by 1 g twice daily for the second day)	**Median duration of episode** 5.0 days with 1-day course of valaciclovir (2 g twice daily) 5.5 days with placebo	P <0.001 for 1-day course of valaciclovir *v* placebo	○○○	valaciclovir
[21] RCT **3-armed trial**	954 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication The third arm evaluated 1-day course of valaciclovir (2 g twice daily)	**Median duration of episode** 5.0 days with 2-day course of valaciclovir (2 g twice daily for the first day followed by 1 g twice daily for the second day) 5.5 days with placebo	P <0.001 for 2-day course of valaciclovir *v* placebo	○○○	valaciclovir
[22] RCT **3-armed trial**	701 people aged 18 years or older with recurrent herpes labialis In review [9] The remaining arm evaluated famciclovir as two doses on 1 day	**Median time to resolution of all vesicular lesions (primary and secondary lesions)** 4.5 days with famciclovir as single dose on 1 day 6.6 days with placebo Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions	P <0.001 for famciclovir as single dose on 1 day *v* placebo Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)	○○○	famciclovir
[22] RCT **3-armed trial**	701 people aged 18 years or older with recurrent herpes labialis In review [9] The remaining arm evaluated famciclovir as single dose on 1 day	**Median time to resolution of all vesicular lesions (primary and secondary lesions)** 4.1 days with famciclovir as two doses on 1 day 6.6 days with placebo Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions	P <0.001 for famciclovir as two doses on 1 day *v* placebo Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)	○○○	famciclovir

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **3-armed trial**	701 people aged 18 years or older with recurrent herpes labialis In review [9]	**Proportion of people with aborted lesions (aborted lesions defined as herpetic lesions not progressing beyond the papule stage** with famciclovir as single dose on 1 day with famciclovir as two doses on 1 day with placebo Absolute results not reported Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions	Difference among groups reported as not significant P value not reported Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)	⟷	Not significant

Recurrence

No data from the following reference on this outcome. [19] [20] [21] [22]

Quality of life

No data from the following reference on this outcome. [19] [20] [21] [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT **3-armed trial**	902 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication	**Headache** 9% with 1-day course of valaciclovir 9% with 2-day course of valaciclovir 4% with placebo	Significance not assessed		
[21] RCT **3-armed trial**	954 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication	**Headache** 10% with 1-day course of valaciclovir 9% with 2-day course of valaciclovir 5% with placebo	Significance not assessed		
[21] RCT **3-armed trial**	902 people aged at least 12 years with recurrent herpes labialis In review [9]	**Nausea** 4% with 1-day course of valaciclovir 5% with 2-day course of valaciclovir	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	One of two RCTs reported in the same publication	4% with placebo			
[21] RCT **3-armed trial**	954 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication	**Nausea** 4% with 1-day course of valaciclovir 4% with 2-day course of valaciclovir 5% with placebo	Significance not assessed		
[21] RCT **3-armed trial**	902 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication	**Diarrhoea** 4% with 1-day course of valaciclovir 3% with 2-day course of valaciclovir 3% with placebo	Significance not assessed		
[21] RCT **3-armed trial**	954 people aged at least 12 years with recurrent herpes labialis In review [9] One of two RCTs reported in the same publication	**Diarrhoea** 2% with 1-day course of valaciclovir 1% with 2-day course of valaciclovir 3% with placebo	Significance not assessed		
[22] RCT **3-armed trial**	701 people aged 18 years or older with recurrent herpes labialis In review [9]	**Headache** 9.7% with famciclovir as single dose on 1 day 7.3% with famciclovir as 2 doses on 1 day 6.7% with placebo Absolute numbers not reported Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions	Significance not assessed Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)		
[22] RCT **3-armed trial**	701 people aged 18 years or older with recurrent herpes labialis In review [9]	**Nausea** 2.2% with famciclovir as single dose on 1 day 2.3% with famciclovir as 2 doses on 1 day 3.9% with placebo Absolute numbers not reported Participants were instructed to self-initiate therapy within 1 hour of the onset of prodromal symptoms and before the appearance of lesions.	Significance not assessed Analysis included only people who subsequently developed vesicular herpes labialis lesions during the course of treatment, which may affect generalisability (see further information on studies for full details)		

No data from the following reference on this outcome. [19] [20]

Further information on studies

[22] In all, 701 people had symptoms of a recurrence and started study medication. However, the analysis only included the 477/701 (68%) of participants who subsequently developed vesicular herpes labialis lesions during the course of treatment. Hence, the results may only apply to those people who develop lesions, rather than all those people with initial prodromal symptoms.

Comment: We found no RCTs comparing early versus delayed intervention, therefore we can draw no firm conclusions about timing of treatment.

OPTION TOPICAL ANTIVIRAL AGENTS FOR TREATING RECURRENT ATTACKS

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- We found limited evidence that topical antiviral agents may reduce pain and healing time in recurrent attacks. However, results are inconsistent and of marginal clinical importance.

Benefits and harms

Topical antiviral agents versus placebo:

We found one systematic review (search date 2008), [9] which found 12 RCTs (published in 11 papers) comparing topical aciclovir or penciclovir versus placebo. [7] [8] [23] [24] [25] [26] [27] [28] [29] [30] [31] The review did not pool data, and did not report a methodological appraisal or a statistical analysis of individual RCTs. Therefore, we have reported the RCTs from their original reports.

Symptom improvement

Topical antiviral agents compared with placebo Topical aciclovir seems no more effective at reducing mean duration of pain. Topical penciclovir seems more effective at marginally reducing median duration of pain (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[7] RCT	61 people In review [9]	**Mean duration of pain** 1.2 days with aciclovir 1.1 days with placebo	Significance not assessed		
[23] RCT	30 people In review [9]	**Mean duration of pain** 1.7 days with aciclovir 2.3 days with placebo	P = 0.53	⟷	Not significant
[24] RCT	208 people In review [9]	**Mean duration of pain** 1.9 days with aciclovir 2.1 days with placebo	P = 0.30	⟷	Not significant
[25] RCT	2209 people In review [9]	**Median duration of pain** 3.5 days with penciclovir cream (twice daily for 4 days) 4.1 days with control cream	P <0.001	○○○	penciclovir cream
[26] RCT	80 people In review [9]	**Mean duration of pain** 1.08 days with aciclovir 1.04 days with placebo	Significance not assessed		

No data from the following reference on this outcome. [8] [27] [28] [29] [30] [31]

Time to healing

Topical antiviral agents compared with placebo Topical aciclovir or topical penciclovir seem more effective at marginally reducing healing time (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[8] RCT **Crossover design**	13 people In review [9]	**Mean healing time** 7 days with aciclovir 8 days with placebo	P <0.05	○○○	aciclovir
[23] RCT	30 people In review [9]	**Mean healing time** 5.7 days with aciclovir 8.3 days with placebo	P = 0.022	○○○	aciclovir
[27] RCT	45 people In review [9]	**Mean healing time** 10 days with aciclovir 13 days with placebo	Reported as not significant P value not reported	⟷	Not significant
[24] RCT	208 people In review [9]	**Mean healing time** 7.2 days with aciclovir 7.2 days with placebo	P = 0.67	⟷	Not significant
[25] RCT	2209 people In review [9]	**Median healing time** 4.8 days with penciclovir cream (twice daily for 4 days) 5.5 days with control cream	P <0.001	○○○	penciclovir
[26] RCT	80 people In review [9]	**Mean healing time** 7.9 days with aciclovir 8.8 days with placebo	Reported as not significant P value not reported	⟷	Not significant
[28] RCT	534 people In review [9]	**Mean healing time of lesions** 7.6 days with 1% penciclovir 8.8 days with placebo	P <0.01	○○○	penciclovir
[29] RCT	380 people In review [9]	**Mean healing time** 9.0 days with aciclovir 10.1 days with placebo	P = 0.04 The RCT was conducted under artificial conditions	○○○	aciclovir
[30] RCT	670 people In review [9] One of two RCTs reported in same publication	**Mean healing time** 4.3 days with aciclovir 4.8 days with placebo	P = 0.010	○○○	aciclovir
[30] RCT	673 people In review [9] One of two RCTs reported in same publication	**Mean healing time** 4.6 days with aciclovir 5.2 days with placebo	P = 0.007	○○○	aciclovir
[31] RCT **3-armed trial**	31 people In review [9] The remaining arm evaluated 5% aciclovir cream	**Mean time to crusting** 1.6 days with 5% aciclovir in a liposomal vehicle 4.8 days with control (drug-free vehicle) 15 people later took part in a crossover study, in which they	P <0.05	○○○	aciclovir in a liposomal vehicle

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		received two forms of topical aciclovir (see further information on studies for full details)			
[31] RCT **3-armed trial**	31 people In review [9] The remaining arm evaluated 5% aciclovir in a liposomal vehicle	**Mean time to crusting** 4.3 days with 5% aciclovir cream 4.8 days with control (drug-free vehicle) 15 people later took part in a crossover study, in which they received two forms of topical aciclovir (see further information on studies for full details)	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [7] [31]

Recurrence

No data from the following reference on this outcome. [7] [8] [23] [24] [25] [26] [27] [28] [29] [30] [31]

Quality of life

No data from the following reference on this outcome. [7] [8] [23] [24] [25] [26] [27] [28] [29] [30] [31]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[7] [8] [23] [24] [25] [26] [27] [28] [29] [30] [31] RCT		**Adverse effects** with antiviral agents with placebo The RCTs found no serious adverse events and reported similar rates of minor adverse events in both treatment groups.			

Further information on studies

[31] A total of 15 people in the RCT later took part in a crossover study, in which they received two forms of topical aciclovir (in random order) separated by a washout period of at least 1 month. The study found that aciclovir in liposomes significantly reduced the time to crusting of lesions compared with aciclovir cream (1.8 days *v* 3.5 days; P = 0.023). In this RCT, too few people experienced pain to enable statistical analysis of the impact of the treatments on discomfort.

Comment: We found no RCTs comparing early versus delayed intervention, therefore we can draw no firm conclusions about timing of treatment.

A number of the smaller trials comparing topical antiviral agents versus placebo found no significant effect of treatment. However, these studies may have lacked power to detect clinically important differences.

OPTION TOPICAL ANAESTHETIC AGENTS FOR TREATING RECURRENT ATTACKS

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- We don't know whether topical anaesthetic agents reduce healing time.

Benefits and harms

Topical anaesthetic agents versus placebo:

We found one systematic review (search date 2008), [9] which found no RCTs of sufficient quality. We found one additional RCT comparing 1.8% tetracaine (amethocaine) cream (applied 6 times daily until scab loss occurred) versus placebo. [32]

Symptom improvement

Topical anaesthetic agents versus placebo Topical tetracaine may be more effective at increasing the proportion of people who subjectively rate the treatment as effective (measured on a 10-point scale); however, the clinical importance of this is unclear (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[32] RCT	72 people	**Subjective treatment benefit index (patient-rated; scale of 1 to 10; 1 = no benefit at all, 10 = very effective treatment)** 7.3 with 1.8% tetracaine cream 5.9 with placebo	P = 0.036 The clinical importance of these results is unclear	○○○	tetracaine

Time to healing

Topical anaesthetic agents versus placebo Topical tetracaine applied daily until scab loss occurs may be more effective at reducing the mean time to scab loss; however, the clinical importance of this is unclear (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[32] RCT	72 people	**Mean time to scab loss** 5.1 days with 1.8% tetracaine cream 7.2 days with placebo	P = 0.002 The clinical importance of these results is unclear	○○○	tetracaine

Recurrence

No data from the following reference on this outcome. [32]

Quality of life

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT	72 people	**Adverse effects** with 1.8% tetracaine cream with placebo No adverse effects as a result of treatment reported.			

Further information on studies

Comment: None.

OPTION ZINC OXIDE CREAM FOR TREATING RECURRENT ATTACKS

- For GRADE evaluation of interventions for Herpes labialis, see table, p 26 .
- We don't know whether zinc oxide cream reduces healing time. Zinc oxide cream may increase skin irritation

Benefits and harms

Zinc oxide cream versus placebo:

We found one systematic review (search date 2008), [9] which found one RCT. [33] The RCT compared zinc oxide/glycine cream versus placebo.

Symptom improvement

No data from the following reference on this outcome. [33]

Time to healing

Zinc oxide cream compared with placebo Zinc oxide/glycine cream applied as soon as possible after the onset of an attack may be more effective at reducing time to healing (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to healing					
[33] RCT	46 people In review [9]	**Time to healing** 5.0 days with zinc oxide/glycine cream (applied twice hourly during waking hours as soon as possible after the onset of an attack) 6.5 days with placebo	P = 0.018	○○○	zinc oxide/glycine cream

Recurrence

No data from the following reference on this outcome. [33]

Quality of life

No data from the following reference on this outcome. [33]

Adverse effects

Zinc oxide cream compared with placebo Zinc oxide/glycine cream may increase the risk of skin irritation (burning) compared with placebo (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] RCT	46 people In review [9]	**Transient mild to moderate sensations of burning** 22% of people with zinc oxide/glycine cream (applied twice hourly during waking hours as soon as possible after the onset of an attack) 7% of people with placebo Absolute numbers not reported All resolved spontaneously	Significance not assessed		
[33] RCT	46 people In review [9]	**Itching** 9% of people with zinc oxide/glycine cream (applied twice hourly during waking hours as soon as possible after the onset of an attack) 4% of people with placebo Absolute numbers not reported All resolved spontaneously	Significance not assessed		
[33] RCT	46 people In review [9]	**Stinging** 3% of peolpe with zinc oxide/glycine cream (applied twice hourly during waking hours as soon as possible after the onset of an attack) 4% of people with placebo Absolute numbers not reported All resolved spontaneously	Significance not assessed		
[33] RCT	46 people In review [9]	**Tingling** 3% of people with zinc oxide/glycine cream (applied twice hourly during waking hours as soon as possible after the onset of an attack) 0% of people with placebo Absolute numbers not reported All resolved spontaneously	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[33] RCT	46 people In review [9]	**Number of people who discontinued** with zinc oxide/glycine cream (applied twice hourly during waking hours as soon as possible after the onset of an attack) with placebo Absolute results not reported Reason for discontinuation was burning with zinc cream and lack of improvement with placebo	Significance not assessed		

Further information on studies

Comment: None.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Oral antiviral agents for treating recurrent attacks One systematic review added (search date 2008), [9] which did not pool data. It identified four RCTs previously reported in this *Clinical Evidence* review, and one additional RCT comparing famciclovir versus placebo not previously reported in this *Clinical Evidence* review. [22] Results from this RCT added from the original report of the RCT. [22] Categorisation unchanged (Likely to be beneficial).

Oral antiviral agents to prevent recurrence One systematic review added (search date 2008), [9] which did not pool data. It found three RCTs and one pooled analysis of two further RCTs that were already reported in this *Clinical Evidence* review. No new data added from the new review. [9] Categorisation unchanged (Likely to be beneficial).

Sunscreen One systematic review added (search date 2008) [9] identifying one small crossover RCT already reported in this *Clinical Evidence* review. No new data added from the new review. [9] Categorisation unchanged (Likely to be beneficial).

Topical anaesthetic agents for treating recurrent attacks One systematic review added (search date 2008), [9] which found no RCTs of sufficient quality. No data added from the new review. Categorisation unchanged (Unknown effectiveness).

Topical antiviral agents for treating recurrent attacks One systematic review added (search date 2008), [9] which did not pool data and identified 12 RCTs already reported in this *Clinical Evidence* review. No new data from the systematic review added. [9] Categorisation unchanged (Unknown effectiveness).

Topical antiviral agents to prevent recurrence One systematic review added (search date 2008), [9] which identified two RCTs. [9] The review did not pool data, and the results of the RCT were reported from the original papers. Benefits and harms section enhanced. Categorisation unchanged (Unknown effectiveness).

Zinc oxide cream for treating recurrent attacks One systematic review added (search date 2008), [9] which identified one RCT previously reported in this *Clinical Evidence* review. No new data added from the review. [9] Categorisation unchanged (Unknown effectiveness).

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Competing interests: GW declares that he has no competing interests.
We would like to acknowledge the previous contributors of this review, including Bazian Ltd.

Disclaimer

GRADE **Evaluation of interventions for Herpes labialis.**

Important outcomes	, Adverse effects, Quality of life, Recurrence, Symptom improvement, Time to healing								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of antiviral treatments for the first attack of herpes labialis?									
1 (20) [4]	Symptom improvement	Oral antiviral agents versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for restricted population (children only)
1 (72) [5]	Time to healing	Oral antiviral agents versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for restricted population (children only)
What are the effects of interventions aimed at preventing recurrent attacks of herpes labialis?									
1 (147) [10]	Symptom improvement	Oral antiviral agents versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (248) [14]	Time to healing	Oral antiviral agents versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and use of experimental exposure to artificial ultraviolet light
6 (752) [10] [11] [12] [13] [14]	Recurrence	Oral antiviral agents versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, exposure to artificial ultraviolet light in 1 RCT, and unclear outcome assessment
1 (90) [15]	Symptom improvement	Topical antiviral agents versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for experimental exposure to artificial ultraviolet light
1 (90) [15]	Time to healing	Topical antiviral agents versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for experimental exposure to artificial ultraviolet light
2 (271) [15] [16]	Recurrence	Topical antiviral agents versus placebo	4	–1	0	–2	0	Very low	Quality point deducted for reporting of results. Directness points deducted for experimental exposure to artificial ultraviolet light and inconsistent results at different time points
2 (57) [17] [18]	Recurrence	Sunscreen versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, short follow-up, and use of experimental exposure to artificial ultraviolet light
What are the effects of treatments for recurrent attacks of herpes labialis?									
3 (800) [19] [20] [22]	Symptom improvement	Oral antiviral agents versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and unclear outcome assessment. Consistency point deducted for different results for different outcomes
4 (2482) [20] [21] [22]	Time to healing	Oral antiviral agents versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results for different outcomes
5 (2588) [7] [23] [24] [25] [26]	Symptom improvement	Topical antiviral agents versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes	, Adverse effects, Quality of life, Recurrence, Symptom improvement, Time to healing								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
10 (4842) [8] [23] [24] [25] [26] [27] [28] [29] [30]	Time to healing	Topical antiviral agents versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (72) [32]	Symptom improvement	Topical anaesthetic agents versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and subjective outcome measure. Directness point deducted for unclear clinical relevance
1 (72) [32]	Time to healing	Topical anaesthetic agents versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear clinical relevance
1 (46) [33]	Time to healing	Zinc oxide cream versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for limited outcomes reported (healing only)
1 (46) [33]	Adverse effects	Zinc oxide cream versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and no statistical comparison between groups

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.